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Review

Autoantibodies as diagnostic markers in cancer

Running title: Autoantibodies in cancer

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Abstract

The emergence of autoantibodies (AAbs) against self-antigens is an old story almost a hundred years old. On the contrary, only recently scientists started to shed light on the antigen-specific immune response in cancerous diseases. During the last decades numerous studies have revealed the significance and applications of autoantibodies in cancer. Cancer-evoked immunity has apparently dual role in either promoting or suppressing the neoplastic progression. Moreover, the implications of AAbs in early diagnosis as biomarkers are continually studied focusing on early detection of cancer and effective management. In this mini review, we mostly elaborate the possible contribution of autoantibodies in the diagnosis of cancer.

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I. INTRODUCTION

Cancer, despise all the scientific developments, remains the second leading cause of death and a still growing public health issue in the whole world.The estimation is that about 1,670 deaths a day are expected to occur in the US (1). Prostate, colorectal, lung, stomach and liver cancer prevail in men while colorectal, lung, breast, thyroid and cervix cancer are the most widespread among women (2).
As such, it is more urgent every day the acquisition of more accurate screening methods for early diagnosis leading to effective treatments and better prognosis. An alternative to the traditional strategies in the battle against cancer is the presence of autoantibodies.

Autoantibodies are immunoglobulins directed against self-antigens (3). The corresponding antigens have an enhanced or abnormal expression in cancer cells than in healthy ones. In 1901 the first report about the AAbs existence came in light and almost 50 years later a report was published about antinuclear antibodies in the serum of patients with Systematic Lupus Erythematosus (SLE) (4–8). These cell-penetrating AAbs which have the ability to intrude into living cells in vitro and in vivo are characteristic findings in autoimmune diseases. A still growing number of AAbs have been discovered against different antigens namely nuclear, cytoplasmic different proteins, cell membrane etc (9).

The whole process of antibody production is still foggy but multiple elements appear to play pivotal roles for example infection, genetic predisposition, ineffective apoptosis and environmental factors etc(9). The pathogenesis of the emergence of the autoantibodies depends on the dysfunction of the immune system in the same platform for autoimmune diseases and cancer. In the context of a defective immune tolerance autoreactive lymphocytes prevail, generate AAbs and cause autoimmunity and cancer with different biologic activities in each entity (10,11). The spontaneous AAbs in neoplasm might represent the effort to fight against tumor progression whereas in autoimmunity it is more of a self tolerance failure and inflammation (12). In 1996 the scientific community acknowledged the report of Baldwin et.al. about the generation of autoantibodies due to tumor-associated antigens (TAAs) presented in cancer cells' surface (10,13). Another class of antigens after epigenetic alterations, mutations or deletions in normal genes so called tumor-specific antigens (TSAs) emerged (14). Escape from immunosurveillance is considered the main

pathophysiological procedure leading to tumor growth but the pathogenic role of autoantibodies is still vague. Researchers strive to exploit AAbs for prompt diagnosis, gain information about tumor progression, target therapies and prognosis to fill the knowledge gap in oncology.

A great number of epidemiological studies focused on the increased or decreased risk of certain types of cancers in autoimmune diseases and on the other hand the promoting role of cancer to induce autoimmunity. So, Rheumatoid Arthritis (RA) has been correlated to increased risk of hematological and solid cancers (15) and on the other side of the spectrum development of Scleroderma in cancer patients having POLR3A mutation (16). AAbs share their presence in cancer as well as in autoimmune diseases like anti-Ro/SS-A and anti-La/ SS-B in patients with Sjogren's syndrome (17) and SLE (18) and in hematological neoplasia as well (12). In cancerous diseases AAbs are frequently detectable after spontaneous B-cell response and might be useful because of their biologic activities to tackle malignancies. Accordingly, in autoimmune diseases AAbs could be useful for diagnosis and disease progression.

In this review, we summarize the current data with regards to the application of AAbs in oncology. There is growing evidence for their ability to contribute as cancer biomarkers in clarification of diagnosis.

2. HUMORAL IMMUNE RESPONSE IN CANCER PROGRESSION

A very significant trait of adaptive immune response in cancer patients is the infiltration of the tumor microenvironment by tumor associated B cells and the consequent immune surveillance within has positive or negative effects in immune responses. In this context, some AAbs promote cancer progression whereas others prevent tumor growth. It has been suggested that there are two potential justifications (19), firstly the presence of the AAbs characterize an immune system in "a good shape" with good prognosis and secondly, they have an immediate impact on the tumor by implicating various mechanisms(20).

In 1970, Sir Frank Mac Farlane Burnet introduced the concept of immune surveillance theory as he proposed that neo-antigens trigger immunological reaction against tumors(21). This function might create better survival rates in different malignancies for instance melanoma (14), Hodgkin lymphoma (22), prostate carcinoma (23), glioblastoma (24), colon carcinoma (25), ovarian (26), gastric (27), pancreatic (28), hepatocellular (29), lung (30), breast cancer (31), tongue (32) cancers. Additionally, some spontaneous induced autoantibodies might constrain cancer tumorigenesis through complement –dependent and antibody-dependent cytotoxicity, antigen-presenting cells(APCs) and T cells activation (33(33) or intervene in functionality of tumor cell surface structures (i.e. receptors). On the contrary, some AAbs may foster malignancy progress. As we aforementioned, cancer and autoimmunity share a plethora of AAbs. Patients with autoimmune diseases might have heightened risk to develop neoplasia and on the other hand cancer patients may easier affected, compared to general population from an autoimmune-related disease.

Patients with Systemic sclerosis (Sc) have been showed that they present high risk for neoplasia especially in breast and lung (34). The published work of the John Hopkins Scleroderma Center database depicted that there is a connection of this augmentation with the presence of autoantibody against RNA-polymerase III subunit (35).Moreover, they revealed mutations in the corresponding gene (POLR3A) strongly suggest the implication in a novel way of cancer in this autoimmune disease (36).In an Italian study, correlation of anti-Scl70 with lung cancer is revealed (37) and additionally Bruni et.al found anti-PM/Scl100 in scleroderma patients with cancer(38).

Another element that is currently under investigation is the subtype of the autoantibody involved in cancer progression. It seems that IgG4 subclass antibodies are taking part in tumor microenvironment and serum IgG4 was inversely correlated with patient survival as Karagiannis et.al suggested in 2013. Their work proposed that IgG4 in Th2-based inflammation may provide a tumor-induced immune escape and a good start for biomarker development and personalized therapeutic approaches (39).

Additionally, a procedure of importance regarding the contribution of AAbs in cancer progression are secreted IgG antibodies from cancer epithelial cells resulting to support promotion and not apoptosis of tumors (40–43).Nevertheless, more effort is needed to elucidate these implications of AAbs in malignancy progression.

3. POTENTIAL EXPLOITATION OF AUTOANTIBODIES AS CANCER BIOMARKERS CONTRIBUTING TO DIAGNOSIS

It is generally accepted that early detection of any type of cancer is the goal of medical approach to mitigate or prevent metastasis and nullify mortality rates. In this context, during the last decades, the generation of AAbs as a characteristic of effective immune surveillance for tumor cells became prominent for cancer screening and diagnosis. The potential implication of autoantibodies as cancer biomarkers have been investigated from many groups since the first antigen, p53, described to trigger AAbs production in breast cancer patients (44). In 1999 Fernandez-Madrid et.al. described antinuclear antibodies in sera of patients with lung cancer and suggested the diagnostic and prognostic value of this finding (45).

The continuously growing interest regarding AAbs as diagnostic tools in cancer has been strengthened by their notable characteristics. On the contrary to the low or even undetectable concentrations of protein biomarkers, B-cell response offers abundant, high affinity antibodies, present in early stages of cancers. Specifically, these biomarkers, as immunoglobulins, are characterized by their stability and persistence in high quantities for prolonged periods in serum samples, due to diminished proteolysis and clearance from the circulation (10,46,47). It is noteworthy that they are easily obtained with minimally invasive technics and they have long half-lives. These traits increase their sensitivity and specificity for diagnosing tumors than antigens. For example, anti-alpha-fetoprotein (AFP) antigen has only 60% and 69% sensitivity and specificity respectively with regards to liver cancer diagnosis compared to AFP antibody sensitivity 89% and specificity 77% (48). Actually, the most intriguing feature of AAbs is their ability to emerge long before the first signs and clinical diagnosis of cancer for months or even years (49).For instance, strong evidence supporting this notion came from studies that revealed the presence of p53 (tumor suppressor protein) AAbs in the sera of smokers and workers in carcinogenic environment prior to development of lung cancer (50,51).Recent studies have elaborated more AAbs in early stages of different types of neoplasia namely prostate (52), ovarian (53), lung (54), gastrointestinal (55), breast (56,57) and cervical (58,59). Having considered all the above cancer serum AAbs might serve as novel cancer biomarkers, after the verification of specific panels with the suitable combination, to indentify tumor signals as early as possible.

Currently, as the research is still ongoing, previous results have made clear that detection of a single cancer biomarker has less value in screening and predict malignancies when compared to panels of circulating autoantibody, especially in tandem with corresponding antigens, which yield to significant diagnostic power. With this approach, to blend together multiple immune responses in a group, it is more thoroughly addressed the diversity of tumor cells antigens. Somiari RI et.al in 2016 and Bassaro L et.al. in 2017 used for this reason an Autoantibody Profiling System-90 containing 90 antigens aiming to detect disease-associated AAbs pertinent to different autoimmune conditions and cancer in human plasma (60,61). Another group employed a panel of four AAbs against human HER2, p53, TOPO2 and IGFBP2(insulin like growth factor binding protein) in breast cancer resulting with 75% specificity and sensitivity(62). More intriguing is the combination of 22-phage-diplayed antigens for prostate neoplasia that achieved 88% sensitivity and 82% specificity (63). The common denominator of the majority of these studies is the insufficient diagnostic sensitivity and specificity which must be addressed by either multiple markers or discovery of novel antibody targets.

Furthermore, scientists strive to exploit novel technologies for AAbs detection. Apart from enzyme linked immunosorbent assay (ELISA) which has drawn a lion's portion in this field for many years along with protein microarrays, novel methodologies have emerged and struggle to insure a place in the future scene. High Throughput methods for autoantibody detection include serological proteome analysis (SERPA)(64,65), Reverse-capture antibody microarray (a modern version of multiplex elisa) (64), Self-assembly microarray(66) , Multiple Affinity Protein Profiling (MAPPing)(67), Phage-display antigen microarrays (Epitomics)(68) and Glycan arrays (67). Moreover, new and unique techniques appear like the nanoplasmonic-based biosensor by Soler M. which offers sensitive and real-time quantification of autoantibodies for the early diagnosis of colorectar cancer (69). It is really pivotal to incorporate high-throughput assays during the exploration procedure to detect specific panels of autoantibodies with specific traits foe early diagnosis. Moreover, validation assays are of paramount importance in order to determine the actual significance of the discovered autoantibodies in clinical practice.(67)

AAbs detection and quantification new methods might be an invaluable diagnostic tool for screening strategies as well for asymptomatic and cancer high-risk groups but with improved sensitivity and specificity in clinical practice.

4. DISCUSSION

It is well-studied up to now that the measurement of spontaneous disease-associated antibodies could provide early detection of neoplasia before the onset of physical symptoms, which would be of paramount importance by offering patients a wider range of options for effective treatment at an earlier stage of disease.

The experience from the autoimmune diseases paves the way to investigate the hidden properties of AAbs. Roughly speaking, some of them could be protective against some cancers while others significantly increase the occurrence of specific cancer types. For example, the risk for expressing lung, pancreatic, hepatic, thyroid, haematological, vulvar neoplasia in SLE patients is heightened comparing to others namely breast, endometrial, ovarian etc.(9). Likewise, patients with RA exhibit increased risk of developing lung cancer as well as leukemia and lymphoma (70) and at the same time a significantly decreased risk for breast, cervical and colon cancer (70,71).

It is more than obvious that there is a still expanding variety of AAbs in cancerous diseases lies on the findings of numerous animal and human studies with more than 120 reported responsible tumor antigens (14) pointing out the unique competence of our immune system to sense the non-

self even among native elements. The pathophysiology of the AAbs' emergence share common features with autoimmune diseases having inflammation in the tumor microenvironment as the cornerstone known already from the 19th century(14).

Experience gained from research have indicated that combination or panels of AAbs are better working as diagnostic biomarkers in lieu of single autoantibodies yet proven from an autoantibody assay, EarlyCDT-Lung.(72) The dissection of single antibody specificities is a difficult task considering the polyclonal nature of B cells by the same manner as autoimmunity(73).

5. CONCLUSIONS

Summarily, in all pathologies early biomarkers represent invaluable tools for the early diagnosis and management. Especially in cancer it is of crucial importance the application of non-invasive, accurate and sensitive methods as early diagnostic tools to detect the emergence of neoplasia.

The study of AAbs against mutated or even normal proteins is alive and kicking. By exploiting the multiple line of evidence from autoimmune diseases research aims at better understanding of the immune response and the intricate nature and specificity of the AAbs against TAAs and TSAs. They might represent promising biomarkers highly stable, circulating for more time than antigens and are present earlier than symptoms for the early diagnosis in cancers(67,74) incorporating the protein array technology and analyzing a great number of proteins simultaneously. There are still open issues regarding the value of AAbs in cancerous diseases but despite many odds, seem to have great potential in early detection and even treatment and prognosis in a personalized way. Maybe the scientific community tackling with autoimmune and cancerous diseases in tandem is ready to kill two birds with one stone.

AUTHORS CONTIBUTION

All authors participated in preparing the final version of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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